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Services**Durrant LG, Spendlove I**

CRC Department of Clinical Oncology, City Hospital, Nottingham, UK.

Publication Types:

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Services**Cell lines transfected with the TAP inhibitor ICP47 allow testing peptide binding to a variety of HLA class I molecules.****Gatfield J, Lammert E, Nickolaus P, Munz C, Rothenfusser S, Fisch P, Stevanovic S, Schild H, Rammensee HG, Arnold D**

Department of Immunology, Institute for Cell Biology, Eberhard-Karls University Tübingen, Germany.

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The immediate early protein ICP47 of the Herpes simplex virus is known to block the human transporter associated with antigen processing (TAP), thereby creating a TAP-deficient phenotype in any human cell transfected with the corresponding cDNA. Exploiting this inhibitory activity, we constructed a selection of human cell lines each co-expressing one of the cDNAs of human leukocyte antigen (HLA) class I alleles HLA-A*1101, A24, A*3101, A*6601, B8 and B*1516, and the cDNA encoding the ICP47 molecule. The cell lines generated showed diminished HLA class I surface expression and the inhibition of the TAP function was confirmed in peptide translocation assays. The addition of specific exogenous peptide ligands restored the expression of the corresponding HLA class I molecules. Thus, the ICP47 transfectants provide us with a tool to closely examine peptide-HLA class I interactions, to confirm HLA class I ligand motifs and to test peptides predicted to bind.

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**Priming in vivo and quantification in vitro of class I
MHC-restricted cytotoxic T cells to human papilloma virus type
11 early proteins (E6 and E7) using immunostimulating complexes
(ISCOMs).**

Tarpey I, Stacey SN, McIndoe A, Davies DH

Division of Life Sciences, King's College, London, UK.

Immunostimulating complexes (ISCOMs) efficiently deliver soluble antigen into both the cytosolic (endogenous) and endosomal (exogenous) pathways of antigen processing. Cytosolic delivery to antigen-presenting cells (APCs) may therefore be useful for the stimulation and assay of class I major histocompatibility complex (MHC)-restricted cytotoxic T lymphocytes (CTL) in vitro. In this study, mice were immunized with ISCOMs containing fusion proteins of the E6 or E7 early proteins of human papilloma virus type 11 (HPV 11) to elicit CTL. These CTL were then restimulated in vitro using APCs pulsed with the same ISCOMs, prior to cytotoxicity assay using syngeneic target cells infected with recombinant vaccinia viruses. In this way, antigen-specific, MHC-restricted lysis by CD8+ cells was detected. However, this was dependent on the use of low density splenocytes as APCs for restimulation in vitro. Limiting dilution analyses showed a direct correlation between the CTL responder frequency and the number of times the animals were immunized in vivo. We conclude that in lieu of infectious virus, the use of ISCOMs to mediate antigen delivery to APCs in vitro can be used to quantitate CTL activity. This may have applications in monitoring vaccine efficacy, particularly to viruses such as HPV, which cannot be presently obtained as infectious virus in sufficient quantity for CTL propagation and assay.

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Cancer vaccines: challenges and potential solutions.PubMed
Services**Hellstrom KE, Gladstone P, Hellstrom I**

Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121, USA.

Almost a century has passed since immunotherapy of cancer was first attempted using cancer immunogens (vaccines); however, its clinical impact remains modest. Although initial concerns about a lack of human tumor antigens have decreased, prevailing issues include inefficient procedures for immunization and downregulated expression of major histocompatibility complex (MHC) class I molecules in tumor cells. While immunization can be improved, deficient MHC class I expression remains a problem, because it hampers the ability of tumor cells to present antigens for killing by CD8+ T cells. These are the major mediators of tumor destruction, and they have little or no activity against antigen-negative bystander cells. However, there are reasons to be optimistic that therapeutic vaccination against cancer antigens might become a reality at last.

PMID: 9257295

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Services**Natural killer cells and recognition of MHC class I molecules: new perspectives and challenges in immunology.****Rolstad B, Seaman WE**Immunology/Arthritis Section, Veterans Administration Medical Center,
University of California, San Francisco 94121, USA.

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Nov;43(3):165-73

**Gene-modified tumor cells as cellular vaccine.**Related Articles, Books,
LinkOut**Baskar S**

Department of Biological Sciences, University of Maryland Baltimore County
21250, USA.

The identification and characterization of many tumor antigens and the parallel explosion of knowledge of the cellular and molecular mechanisms of antigen recognition by the immune system have given renewed hopes that immunogenethrapy could be a promising modality to treat certain tumors. Many different novel strategies have been developed to derive genetically modified tumor cells and use them as cellular vaccines to induce useful antitumor immunity in a variety of animal tumor models. This review discusses induction of tumor immunity by injecting tumor cells that are genetically engineered to secrete various cytokines and to express major histocompatibility complex molecules and/or costimulatory molecules. While there has been a great success in inducing excellent antitumor immunity in a variety of tumor models, there are some difficulties and limitations in the application of these gene-modified tumor cells for the treatment of preexisting tumors. A number of improvements and modifications are already underway to overcome some of these problems.

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Services**Quantitative flow cytometric analysis of the effects of cetirizine on the expression of ICAM-1/CD54 on primary cultured nasal cells.****Mincarini M, Cagnoni F, Canonica GW, Cordone G, Sismondini A, Semino C, Pietra G, Melioli G**

Servizio di Allergologia ed Immunologia Clinica, DIMI, Universita di Genoa, Italy.

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An in vitro flow cytometric model has been developed to evaluate the effects of antiallergic drugs such as cetirizine (CTZ) on the expression of surface molecules on primary cultured normal cells. Quantitative analysis demonstrated that HLA class I and ICAM-1/CD54 molecules are present on both epithelial and stromal cells, and that their expression is strongly enhanced by treatment with interferon-gamma (IFN-gamma). Nevertheless, the IFN-gamma-mediated upregulation of ICAM-1/CD54 was inhibited by treatment with CTZ, demonstrating a direct effect on both cell types. This finding is particularly interesting because ICAM-1/CD54 is the main rhinovirus receptor, and rhinoviruses are the principal cause of asthma exacerbation in children. Thus, according to data derived from this in vitro model, CTZ should have an important role in the reduction of infectious exacerbation of asthma in atopic patients.

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Services**In vitro and in vivo immunomodulatory effects of RDP1258, a novel synthetic peptide.****Magee CC, Azuma H, Knoflach A, Denton MD, Chandraker A, Iyer S, Buelow R, Sayegh M**

Laboratory of Immunogenetics and Transplantation, Brigham & Women's Hospital, Boston, Massachusetts 02115, USA.

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Peptides derived from certain regions of human class I MHC molecules are known to have immunomodulatory effects. In particular, amino acid residues 75-84 of the HLA-B7 and HLA-B2702 molecules have demonstrated allele nonspecific immunosuppression in several animal transplant models. There is evidence that these effects are mediated by binding to intracellular heat shock proteins, including heme oxygenase-1. A new derivative of these peptides, RDP1258, was developed using a novel computer-assisted rational design technique. In vitro, RDP1258 peptide inhibited rat heme oxygenase activity in a dose-dependent manner. Similar to observations made with other in vitro heme oxygenase inhibitors, in vivo administration of RDP1258 peptide to naive rats resulted in upregulation of splenic heme oxygenase activity. The effects of the peptide on alloimmune responses were then tested. Addition of RDP1258 to rat and human mixed leukocyte reactions inhibited proliferation in a dose-dependent manner. In a rat renal transplantation model, peptide therapy combined with a sub-therapeutic dose of cyclosporin A significantly prolonged allograft survival. These data provide further evidence that modulation of the heat shock protein heme oxygenase by rationally designed peptides affects immune effector functions and may allow the development of novel immunomodulatory strategies in organ transplantation.

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Services**The identification of cancer antigens: impact on the development of cancer vaccines.****Rosenberg SA**

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.

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Resources☐ 1: *Vaccine* 2000 Jul 15;18(27):3152-65[Related Articles, Books, LinkOut](#)**Anti-major histocompatibility complex antibody responses in macaques via intradermal DNA immunizations.****Dela Cruz CS, MacDonald KS, Barber BH**

Institute of Medical Sciences, Medical Sciences Building, University of Toronto,
1 King's College Circle, Ontario, M5S 1A8, Toronto, Canada.

In simian immunodeficiency virus (SIV) models, immunization of macaques with uninfected human cells or human major histocompatibility complex (MHC) proteins can induce xenogeneic immune responses which can protect the animals from subsequent SIV challenges. These studies suggest that the induction of anti-MHC immune responses can be a viable vaccine strategy against human immunodeficiency virus type 1 (HIV-1). We have previously shown in mouse studies that DNA immunization with class I and class II MHC-encoding plasmids can elicit both xenogeneic and allogeneic antibody responses against conformationally intact MHC molecules (*Vaccine* 17 (1999) 2479-92). Here we take these observations one step closer to human applications and report that intradermal needle immunizations of non-human primates with plasmid DNA encoding human MHC alleles can safely elicit xenogeneic anti-MHC antibody responses. Moreover, injecting macaques with DNA encoding a specific macaque allogeneic MHC induced anti-allogeneic MHC antibodies production. These studies show that DNA immunization with MHC-encoding vectors can indeed be used to induce specific anti-human xenogeneic, as well as anti-macaque allogeneic MHC immunity in non-human primates. This strategy could thus be used to mobilize anti-MHC antibody response which may be useful as part of an anti-HIV-1 vaccination approach.

PMID: 10856795

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1: *J Immunol* 2000 Jan 15;164(2):805-11

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Services**Human cytomegalovirus gene products US3 and US6 down-regulate trophoblast class I MHC molecules.****Jun Y, Kim E, Jin M, Sung HC, Han H, Geraghty DE, Ahn K**

Graduate School of Biotechnology, Korea University, Seoul, Korea.

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The epidemiological correlation between human CMV (HCMV) infection and spontaneous fetal loss has been suggested, but the underlying mechanism is not well understood. Fetal cytotrophoblasts, which are in direct contact with the maternal immune system in the uterus during pregnancy, do not express HLA-A and HLA-B, but express the nonclassical class I HLA-G and HLA-C. It has been shown that both HLA-G and HLA-C are capable of inhibiting NK-mediated cell lysis. In our present study, using human trophoblast cell lines as well as other cell lines stably transfected with the human class I genes, we have demonstrated that HCMV US3 and US6 down-regulate the cell-surface expression of both HLA-G and HLA-C by two different mechanisms. HCMV US3 physically associates with both trophoblast class I MHC species, retaining them in the endoplasmic reticulum. In contrast, HCMV US6 inhibits peptide transport by TAP and thus specifically the intracellular trafficking of class I molecules. Therefore, these findings suggest for the first time a possible molecular mechanism underlying HCMV-related spontaneous pregnancy loss.

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Human cytomegalovirus gene products US3 and US6 down-regulate trophoblast class I MHC molecules.

J Immunol. 2000 Jan 15;164(2):805-11.

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- ☐ 2: Colonna M, Samaridis J, Cella M, Angman L, Allen RL, O'Callaghan CA, Dunbar R, Ogg GS, Cerundolo V, Rolink A.

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J Immunol. 1998 Apr 1;160(7):3096-100.

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J Exp Med. 1997 Feb 3;185(3):385-91.

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Services**Transloading of tumor cells with foreign major histocompatibility complex class I peptide ligand: a novel general strategy for the generation of potent cancer vaccines.****Schmidt W, Steinlein P, Buschle M, Schweighoffer T, Herbst E, Mechtler K, Kirlappos H, Birnstiel ML**

Research Institute of Molecular Pathology (I.M.P.), Vienna, Austria.

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The major hurdle to be cleared in active immunotherapy of cancer is the poor immunogenicity of cancer cells. In previous attempts to overcome this problem, whole tumor cells have been used as vaccines, either admixed with adjuvant(s) or genetically engineered to express nonself proteins or immunomodulatory factors before application. We have developed a novel approach to generate an immunogenic, highly effective vaccine: major histocompatibility complex (MHC) class I-positive cancer cells are administered together with MHC class I-matched peptide ligands of foreign, nonself origin, generated by a procedure we term transloading. Murine tumor lines of the H2-Kd or the H2-Db haplotype, melanoma M-3 and B16-F10, respectively, as well as colon carcinoma CT-26 (H2-Kd), were transloaded with MHC-matched influenza virus-derived peptides and applied as irradiated vaccines. Mice bearing a deposit of live M-3 melanoma cells were efficiently cured by this treatment. In the CT-26 colon carcinoma and the B16-F10 melanoma, high efficacies were obtained against tumor challenge, suggesting the universal applicability of this new type of vaccine. With foreign peptide ligands adapted to the requirements of a desired MHC class I haplotype, this concept may be used for the treatment of human cancers.

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